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Comparative efficacy between clozapine and other atypical antipsychotics on depressive symptoms in patients with schizophrenia: Analysis of the CATIE Phase 2E data

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Abstract

Background—The comparative antidepressant effects of clozapine and other atypical antipsychotics for schizophrenia remain elusive, leading us to examine this question using the data from the Clinical Antipsychotic Trials of Interventions Effectiveness phase 2E.

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Contributors: S. Nakajima, H. Takeuchi, G. Fervaha, and A. Graff-Guerrero designed the study and wrote the protocol. S. Nakajima managed the literature searches and analyses. S. Nakajima and H. Takeuchi undertook the statistical analysis, and S. Nakajima wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Methods—Ninety-nine patients who discontinued treatment with olanzapine, quetiapine, risperidone, or ziprasidone because of inadequate efficacy were randomly assigned to open-label treatment with clozapine (n=49) or double-blind treatment with another atypical antipsychotic not previously received in the trial (olanzapine [n=19], quetiapine [n=15], or risperidone [n=16]). The primary outcome was the Calgary Depression Scale for Schizophrenia (CDSS) total score. Antidepressant effects of clozapine and the other atypical antipsychotics were compared in patients with chronic schizophrenia and those with a major depressive episode (MDE) at baseline (i.e. ≥6 on the CDSS), using mixed models.

Results—No differences in the baseline CDSS total scores were found between the treatment groups regardless of presence of an MDE. Clozapine was more effective than quetiapine in antidepressant effects for chronic schizophrenia ($p<.01$ for the whole sample and $p=.01$ for those with an MDE), and comparable to olanzapine and risperidone.

Conclusion—The present findings suggest clozapine demonstrates superior antidepressant effects to quetiapine and comparable effects to olanzapine and risperidone in chronic schizophrenia regardless of presence of MDE. Given the indication of clozapine for treatment-resistant schizophrenia (TRS) and the negative impacts of depressive symptoms on clinical outcomes in schizophrenia, further research is warranted to investigate antidepressant effects of clozapine in TRS with an MDE.

Keywords

schizophrenia; depression; clozapine; quetiapine; CATIE

Introduction

The prevalence of depressive symptoms in schizophrenia is reported to range from 25% to 81% (Siris, 2001). They can occur at any time during the course of the illness (Sands and Harrow, 1999) and are associated with worse quality of life (Reine et al., 2003), subjective well-being (Kim et al., 2014), and overall life satisfaction (Fervaha et al., 2013). They are also related to increased risk of suicide (Siris, 2001), psychotic relapse, and psychiatric hospitalization (Tollefson et al., 1999). Consistent with these findings, depressive symptoms serve as a prognostic indicator of poor recovery and reintegration into the community (Resnick et al., 2004).

Clozapine is considered to be the most effective antipsychotic for treatment-resistant schizophrenia (TRS) among currently available atypical antipsychotics (Leucht et al., 2013; Leucht et al., 2009; McEvoy et al., 2006). It is also unique in that it is the only antipsychotic that has demonstrated superior efficacy in individuals with schizophrenia and concomitant suicidal ideation (Meltzer et al., 2003). However, it remains unclear whether clozapine is more effective than other atypical antipsychotics in treating depressive symptoms per se in schizophrenia. To our knowledge, there have been four randomized controlled trials (RCTs) to date comparing the effects of atypical antipsychotics, including clozapine, on depressive symptoms in patients with schizophrenia. Three of these trials are, as well, double- blind. Breier et al. (1999) found that clozapine was superior to risperidone, as assessed by change in the Hamilton Depression Rating Scale total score, over 6 weeks in patients with

schizophrenia who showed poor response to previous antipsychotic treatment (n = 29) (Breier et al., 1999). Azorin et al. (2001) also reported that clozapine was numerically superior to risperidone, as assessed by the change in the Calgary Depression Scale for Schizophrenia (CDSS) total score, over 12 weeks in a similar population (n = 273) (Azorin et al., 2001). Lindenmayer et al. (2004) conducted a 14-week trial, which revealed no difference among clozapine, olanzapine, and risperidone in improving the depression/anxiety factor of the Positive and Negative Syndrome Scale in patients with TRS (n = 157) (Lindenmayer et al., 2004). In a final trial which was open label and 12 weeks in duration, Lewis et al. (2006) reported no difference in change in the CDSS total score among clozapine and other atypical antipsychotics (risperidone, olanzapine, quetiapine, and amisulpride) in TRS (n = 136) (Lewis et al., 2006). These inconsistent results must also be weighed in the context of study limitations that include short follow-up durations (Azorin et al., 2001; Breier et al., 1999; Lewis et al., 2006; Lindenmayer et al., 2004), high antipsychotic doses (e.g. 9 [standard deviation (SD) = 4] mg/day (Azorin et al., 2001) and 11.6 [SD = 3.2] mg/day (Lindenmayer et al., 2004) for risperidone), and variability in rating scales specific to depressive symptoms (Lindenmayer et al., 2004).

The Clinical Antipsychotic Trials of Interventions Effectiveness (CATIE) phase 2E compared the effectiveness of clozapine (open-label treatment) and other atypical antipsychotics (double-blind treatment with olanzapine, quetiapine, or risperidone) in patients with chronic schizophrenia who had discontinued treatment with an atypical antipsychotic (olanzapine, quetiapine, risperidone, or ziprasidone) because of an inadequate response (McEvoy et al., 2006). Strengths of this study include the fact that subjects were followed for a longer period of time; in addition, it can be argued that antipsychotic doses employed are more in line with current recommendations. With this as background, we chose to use data from the CATIE phase 2E to examine the comparative efficacy of clozapine and other atypical antipsychotics (olanzapine, quetiapine, or risperidone) in treating depressive symptoms in patients with chronic schizophrenia.

Methods

Study Design and Participants

The CATIE, funded by the National Institute of Mental Health, compared the effectiveness of atypical antipsychotics and perphenazine in patients with schizophrenia; details of the study are reported elsewhere (Lieberman et al., 2005; McEvoy et al., 2006; Stroup et al., 2003). Briefly, 1493 patients with non-TRS were randomized to olanzapine, risperidone, ziprasidone, quetiapine, or perphenazine under double-blind conditions (phase 1). Patients were excluded if they had a diagnosis of schizoaffective disorder or mental retardation or other cognitive disorders, an unstable serious medical condition, past adverse reactions to a proposed treatment, or TRS or if they were in their first episode of schizophrenia, pregnant, or breastfeeding. Patients who discontinued treatment with perphenazine in phase 1 could enter a trial involving random assignment to olanzapine, quetiapine, or risperidone (phase 1B). In phase 2E, 99 patients who discontinued the treatment in phase 1 or 1B because of inadequate efficacy were randomly assigned to open-label treatment with clozapine (n = 49) or double-blind treatment with another atypical antipsychotic not previously received in the

trial (olanzapine [n = 19], quetiapine [n = 15], or risperidone [n = 16]) (please see Figure 1 in McEvoy et al., 2006 for the detailed study design) (McEvoy et al., 2006). The dose ranges of olanzapine, quetiapine, and risperidone were 7.5–30 mg/day, 200–800 mg/day, and 1.5–6.0 mg/day, respectively. The schedule for dose titration and the maintenance doses were determined by the treating clinicians (McEvoy et al., 2006). Monitoring for agranulocytosis and myocardial inflammation was standardized (McEvoy et al., 2006). The subjects received the treatment for up to 18 months (including time in phases 1, 1B, and 2E) or until they completed 6 months of treatment in phase 2E, unless treatment was discontinued for any reason (i.e. inadequate therapeutic benefit, intolerable side effects, or their own decision). Reasons for discontinuation in Phase 2E have been previously reported (McEvoy et al., 2006).

Outcome Measures

Depressive symptoms were assessed using the CDSS (Addington et al., 1990). The CDSS is a measure of depression specifically designed to assess depressive symptoms separately from negative symptoms in patients with schizophrenia (Addington et al., 1994). It has been validated in independent studies and recommended as the gold standard for assessing depression in schizophrenia for clinical trials (Addington et al., 2010; Collins et al., 1996; Kontaxakis et al., 2000). The Positive and Negative Syndrome Scale (PANSS) were used to assess severity of schizophrenia symptoms (Kay et al., 1987).

Statistical Methods

The primary analysis population in this study was an intent-to-treat (ITT) sample; accordingly, randomly assigned patients who received at least one dose of study medication were included. Following the classification utilized by McEvoy et al. (2006), time was classified into quarterly intervals of phase 2 treatment, represented by months 0, 3, 6, 9, and 12 (McEvoy et al., 2006). End-of-phase assessments were assigned to the next interval. Months 9 and 12 were excluded from statistical testing because of small group sizes.

The primary outcome measure was the CDSS total score. Baseline CDSS total scores were compared among the antipsychotic treatment groups by a Kruskal-Wallis H test. The rates of those who received antidepressants at baseline and during this study were compared among antipsychotic treatment groups by a Fisher's exact test. The imipramine equivalent dose of antidepressants (Inagaki et al., 2012) in those who took them during this study were compared among antipsychotic treatment groups by a one-way analysis of variance. A mixed-effect model for repeated measurements (MMRM) analysis was employed for the comparisons of CDSS total scores among the antipsychotic treatments. More specifically, the model included CDSS total scores as a response variable; the treatment group (clozapine, olanzapine, quetiapine, or risperidone), month, treatment-by-month interaction, and phase 2E baseline CDSS total score-by-month interaction as fixed effects; presence of exacerbation in the 3 months before entering the study and phase 2 baseline CDSS total score as covariates; and patient-specific intercept and slope of month as random effects. All post-randomization measurements of the CDSS total scores were included in the analysis (with no imputation of missing data). If the overall test was significant at a two-tailed p-value for treatment-by-month interaction of $< .05$, clozapine was compared with the other

three atypical antipsychotics using a Hochberg adjustment for multiple comparisons in which the smallest p-value was compared to .05/3 = .017 and the largest to p-value = .05. The same analyses were conducted for patients with a baseline score of ≥ 6 on the CDSS, which was operationalized as meeting CDSS criteria indicative of a major depressive episode (MDE) (Addington et al., 2010). This level of depression has been previously identified as an appropriate cut-off for the prediction of a major depressive disorder, with a specificity of 77% and sensitivity of 92% (Addington et al., 1993). All statistical analyses were obtained using IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY).

Results

Baseline clinical characteristics

The phase 2E baseline demographic and clinical characteristics, and antipsychotic treatment outcomes have been described in detail elsewhere (McEvoy et al., 2006). Mean modal doses (SD) were 332.1 (156.9) mg/day for clozapine, 23.4 (7.9) mg/day for olanzapine, 642.9 (195.0) mg/day for quetiapine, and 4.8 (1.3) mg/day for risperidone, respectively. No significant differences were found in the rates of those who received antidepressants among the antipsychotic treatment groups at baseline (p = .60; Clozapine 33.3%, olanzapine 31.6%, quetiapine 42.9%, and risperidone 50.0%) and during this study (p = .83; Clozapine 37.5%, olanzapine 42.1%, quetiapine 42.9%, and risperidone 50.0%). There was no significant difference in the imipramine equivalent dose of antidepressants in those who took them among the antipsychotic treatment groups during this study ($F(3,36) = 0.90$, p = .45; 107.6 [76.6] mg/day for clozapine, 152.0 [55.1] mg/day for olanzapine, 105.0 [70.4] mg/day for quetiapine, and 135.6 [77.9] mg/day for risperidone).

Comparisons of CDSS total scores among the antipsychotic treatments in the ITT sample

A total of 89 patients was included in the ITT sample of patients with chronic schizophrenia (clozapine [n = 45], olanzapine [n = 17], quetiapine [n = 13], risperidone [n = 14]). No significant difference in baseline CDSS total scores was found among the antipsychotic treatment groups (p = .42). There was, though, a significant difference in treatment efficacy for depressive symptoms among the antipsychotic treatment groups (p = .01) (Table 1); compared with quetiapine, clozapine demonstrated superior efficacy (p < .01). We considered the possibility that a specific anti-suicidal effect of clozapine may contribute to this superiority (Kasckow et al., 2011), and therefore compared the CDSS suicide item scores between the treatment groups. However, we found no significant difference in the anti-suicidal effect between clozapine and quetiapine (p = .77). Moreover, we conducted MMRM analyses to compare effects of these drugs on individual item of the CDSS. We found that clozapine demonstrated superior effect over quetiapine on the CDSS items of depression (p < .01), hopelessness (p = .01), self-depreciation (p = .01), guilty ideas of reference (p < .01), pathological guilt (p < .01), morning depression (p = .02), and observed depression (p = .01). Further, considering the likelihood that improvement in depressive symptoms may be influenced by that in positive or negative symptoms (Tollefson et al., 1998), we calculated Pearson product-moment correlation coefficients between changes in the CDSS and PANSS Positive or Negative score in the clozapine group, using the last observation carried forward (LOCF). However, no correlation was found between changes

in the CDSS and PANSS Positive or Negative score (r = 0.04, p = .81; r = 0.15, p = .32, respectively). No significant differences in treatment efficacy for depressive symptoms were found between clozapine and olanzapine (p = .15) or clozapine and risperidone (p = .39). As exploratory analyses, the other treatment groups were compared using MMRM analysis. No significant differences in efficacy for depressive symptoms were found between olanzapine and quetiapine (p = .29), olanzapine and risperidone (p = .58), or quetiapine and risperidone (p = .22).

Comparisons of CDSS total scores among the antipsychotic treatments in the MDE sample

In the ITT sample, 41 patients presented with MDE at baseline (46.1%; clozapine [n = 18], olanzapine [n = 9], quetiapine [n = 7], risperidone [n = 7]). No significant difference in baseline CDSS total scores was found among the antipsychotic treatment groups (p = .36) (Table 2). No significant differences were found in the rates of those who received antidepressants among the antipsychotic treatment groups at baseline (p = .90; Clozapine 55.6%, olanzapine 44.4%, quetiapine 37.5%, and risperidone 50.0%) and during this study (p = .90; Clozapine 55.6%, olanzapine 55.6%, quetiapine 37.5%, and risperidone 50.0%). There was no significant difference in the imipramine equivalent dose of antidepressants in those who took them among the antipsychotic treatment groups during this study ($F(3,18) = 1.32$, p = .30; 87.5 [71.9] mg/day for clozapine, 157.2.0 [66.3] mg/day for olanzapine, 120.0 [103.9] mg/day for quetiapine, and 153.8 [69.7] mg/day for risperidone). Notably, results closely paralleled what we observed in the larger sample. There was a significant difference in treatment efficacy for depressive symptoms among the antipsychotic treatment groups (p = .01) (Table 2); compared with quetiapine, clozapine demonstrated superior efficacy in treatment of depressive symptoms (p = .01). Comparing CDSS suicide item score between these treatment groups, there was no significant difference in anti-suicidal effects between clozapine and quetiapine (p = .07). By comparison of effects of these drugs on individual item of the CDSS, we found that clozapine demonstrated superior effect over quetiapine on the CDSS items of depression (p < .01), hopelessness (p = .02), self-depreciation (p < .01), guilty ideas of reference (p = .01), and pathological guilt (p = .02). Further, calculating Pearson product-moment correlation coefficients between changes in the CDSS and PANSS Positive or Negative score with the LOCF, no correlation was found between changes in the CDSS and PANSS Positive or Negative score (r = 0.30, p = .23; r = 0.47, p = .05, respectively) in the clozapine group. No significant differences in treatment efficacy for depressive symptoms were found between clozapine and olanzapine (p = .18) or clozapine and risperidone (p = .49). As exploratory analyses, the other treatment groups were once again compared using MMRM analysis. In this case, there was a significant difference between olanzapine and risperidone (p = .01) but not between olanzapine and quetiapine (p = .18) or quetiapine and risperidone (p = .06).

Discussion

This study found that clozapine was more effective than quetiapine for the long-term treatment of depressive symptoms in patients with chronic schizophrenia with or without a diagnosis of MDE, whereas clozapine was comparable to olanzapine and risperidone. The present findings also indicate that this was not attributable to clozapine's specific anti-

suicidal effects (Meltzer et al., 2003; Meltzer and Okayli, 1995). Instead, superior effects of clozapine over quetiapine on core depressive symptoms (i.e. depression, hopelessness, self-depreciation, guilty ideas of reference, and pathological guilt) may contribute to this advantage according to the analyses of individual items in the CDSS (Bech et al., 1975; Gibbons et al., 1993; Maier et al., 1985). In addition, the notion that clozapine's superior antidepressant effects over quetiapine may result from its superiority in alleviating positive or negative symptoms was not supported in the present study. However, Meltzer et al., (2003) noted that clozapine (n = 490) is superior to olanzapine (n = 490) in preventing suicide attempts in patients with schizophrenia at high risk for suicide. The subjects in this current study were not exclusively with high suicidality and the sample size was relatively smaller, which may result in no difference between clozapine and olanzapine in terms of antidepressant effect. What pharmacological attributes might account for this is unclear; notably, these two drugs share similar pharmacokinetic and pharmacodynamic profiles including a relatively short plasma half-life and higher affinity for serotonin 5-HT_2 receptor than for dopamine D_2 receptor (Seeman, 2002).

To our knowledge, this is also the first RCT comparing the antidepressant effects of clozapine and other atypical antipsychotics in patients with schizophrenia meeting surrogate criteria for MDE. In line with the findings from the larger ITT sample, clozapine proved superior to quetiapine in this population while it was comparable to olanzapine and risperidone. Exploratory analyses suggested that risperidone may be more effective than olanzapine in improving depressive symptoms in chronic schizophrenia with MDE. However, two randomized, double-blind, RCTs comparing olanzapine and risperidone in chronic schizophrenia with concomitant MDE (Addington et al., 2010) and post-psychotic depression (Dollfus et al., 2005), respectively, reported no differences in antidepressant effects between these agents. The small sample size associated with our exploratory findings suggests caution in any interpretation of these results.

To this last point, there are limitations relevant to the study as a whole that warrant comment. This reanalysis was based on the CATIE phase 2E study, which itself has a relatively small sample size (n = 99); moreover, the primary outcome measure was not depressive symptoms. The design is naturalistic and patients were treated with clozapine in an open label fashion, with no placebo arm included. Given clozapine's unique role vis-à-vis TRS, we suggest that its comparability with other antipsychotics regarding depressive symptoms be framed accordingly. Just as a distinction between depressive symptoms and MDE is important, it would prove useful to ask this question in schizophrenia but also those who meet specific criteria for TRS. Notwithstanding the limitations of a non-specific scale such as the Brief Psychiatric Rating Scale, results of the seminal study highlighting clozapine's clinical superiority in TRS demonstrated superiority for positive and negative, but not depressive, symptoms (Kane et al., 1988). What is warranted, though, is blinded RCTs that specifically examine specific symptom domains in TRS, including depression, utilizing scales that more reliably tap into the different domains (e.g. CDSS for depression). Furthermore, this study adopted CDSS score of ≥ 6 as a criterion indicative of MDE consistent with previous work examining the effect of antipsychotics on depressive symptoms in the CATIE sample (Addington et al., 2010). However, since this criterion did not include the number and duration of depressive symptoms, it does not necessarily align

with MDE criteria as outlined in the DSM-5 (American Psychiatric Association, 2013). Finally, this study did not examine cost-effectiveness of the atypical antipsychotics on depressive symptoms in schizophrenia. Given clozapine's potentially serious adverse events such as agranulocytosis, further research is needed to compare total health costs and quality-adjusted life year ratings between clozapine and other atypical antipsychotics (Rosenheck et al., 2006).

In conclusion, the present study demonstrated that clozapine may have superior antidepressant effects versus quetiapine in patients with chronic schizophrenia with or without MDE, in contrast to comparable effects with olanzapine and risperidone. One previous report from the CATIE study group on these data, reported that clozapine was more efficacious in reducing overall symptoms, and specifically general psychopathology symptoms, which include depressive symptoms, compared with quetiapine (McEvoy et al., 2006). The present study extends these results by demonstrating that clozapine is superior to quetiapine in reducing depressive symptoms in particular. Arguably, much of the focus to date with clozapine has been in relation to positive, negative, and cognitive symptoms; however, depressive symptoms have been reported to worsen clinical outcomes in patients with schizophrenia, including quality of life and subjective well-being, which in turn increases risk of suicide, relapse, and psychiatric hospitalization (Kim et al., 2014; Reine et al., 2003; Resnick et al., 2004; Sands and Harrow, 1999; Tollefson et al., 1999).

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Table 1

Comparison of antipderessant effects among clozapine and the other atypical antipsychotics in patients with chronic schizophrenia

	Clozapine (n = 45)		Overall treatment difference		Olanzapine (n = 17)				Quetiapine (n = 13)			
	Mean	**SE**	**MMRM**	**P**	**Mean**	**SE**	**MMRM (vs. clozapine)**	**P**	**Mean**	**SE**	**MMRM (vs. clozapine)**	**P**
CDSS total score at baseline	5.4	0.4	Treatment	**.01**	5.4	0.6	Treatment	.06	5.5	0.7	Treatment	**< .01**
CDSS total score at Month 3	4.4	0.4	Month	**.01**	5.3	0.6	Month	.23	5.3	0.8	Month	**.04**
CDSS total score at Month 6	3.3	0.5	Treatment-by-month	**.01**	5.2	0.8	Treatment-by-month	.15	8.2	0.9	Treatment-by-month	**< .01**

	Risperidone (n = 14)			
	Mean	**SE**	**MMRM (vs. clozapine)**	**P**
CDSS total score at baseline	5.4	0.7	Treatment	.14
CDSS total score at Month 3	5.9	0.7	Month	.19
CDSS total score at Month 6	4.4	1.1	Treatment-by-month	.39

Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS). Baseline CDSS total scores were compared among the antipsychotic treatment groups by a Kruskal-Wallis H test. A mixed-effect model for repeated measurements (MMRM) analysis was employed for the comparisons of CDSS total scores among the antipsychotic treatments. If the overall test was significant at a two-tailed p-value for treatment-by-month interaction of < .05, clozapine was compared with the other three atypical antipsychotics with a Hochberg adjustment for multiple comparisons in which the smallest p-value was compared to .05/3 = .017 and the largest to p-value = .05. No significant difference in the baseline CDSS total scores was found among the antipsychotic treatment groups ($\chi 2$ (3) = 2.82, p = .42). There was a significant difference in the treatment efficacy for depressive symptoms among the antipsychotic treatment groups in patients with chronic schizophrenia. Compared with quetiapine, clozapine showed superior efficacy for the treatment of depressive symptoms in this population. Bold number: $p < 0.05$. SE = standard error.

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Table 2

Comparison of antipderessant effects among clozapine and the other atypical antipsychotics in patients with chronic schizophrenia who presented with a major depressive episode

	Clozapine (n = 18)		Overall treatment difference		Olanzapine (n = 9)				Quetiapine (n = 7)			
	Mean	SE	MMRM	P	Mean	SE	MMRM (vs. clozapine)	P	Mean	SE	MMRM (vs. clozapine)	P
CDSS total score at baseline	9.8	0.7	Treatment	.10	9.7	1.0	Treatment	.06	9.7	1.2	Treatment	.12
CDSS total score at Month 3	7.9	0.7	Month	.36	9.1	1.0	Month	.25	6.4	1.2	Month	.40
CDSS total score at Month 6	5.4	0.9	Treatment-by-month	**.01**	9.3	1.7	Treatment-by-month	.18	13.1	1.8	Treatment-by-month	**.01**

	Risperidone (n = 7)			
	Mean	SE	MMRM (vs. clozapine)	P
CDSS total score at baseline	9.9	1.2	Treatment	.47
CDSS total score at Month 3	8.1	1.2	Month	.96
CDSS total score at Month 6	2.7	2.2	Treatment-by-month	.49

Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS). A major depressive episode (MDE) was defined as a baseline score of ≥ 6 on the CDSS. Baseline CDSS total scores were compared among the antipsychotic treatment groups by a Kruskal-Wallis H test. A mixed-effect model for repeated measurements (MMRM) analysis was employed for the comparisons of CDSS total scores among the antipsychotic treatments. If the overall test was significant at a two-tailed p-value for treatment-by-month interaction of < .05, clozapine was compared with the other three atypical antipsychotics with a Hochberg adjustment for multiple comparisons in which the smallest p-value was compared to .05/3 = .017 and the largest to p-value = .05. No significant difference in baseline CDSS total scores was found among the antipsychotic treatment groups in patients with chronic schizophrenia who presented a baseline MDE ($\chi 2$ (3) = 3.20, p = .36). There was a significant difference in the treatment efficacy for depressive symptoms among the antipsychotic treatment groups in patients with chronic schizophrenia. Compared with quetiapine, clozapine showed superior efficacy for the treatment of depressive symptoms in this population. Bold number: $p < 0.05$. SE = standard error.